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(71) Applicant(s)
Novartis AG
(Incorporated in Switzerland)
Schwarzwaldallee 215, 4058 Basel, Switzerland

(72) Inventor(s)
Martin Jackman

(74) Agent and/or Address for Service
B A Yorke & Co
Coomb House, 7 St John's Road, Isleworth,
Middlesex, TW7 6NH, United Kingdom

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EP 0474126 A1 EP 0027286 A2 WO 95/11039 A1

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(54) Abstract Title
Stabilisation of Macrolide Compositions

(57) A pharmaceutical composition for topical application comprising a macrolide, preferably rapamycin or a macrolide of the FK 506 class, is stabilised by the presence of an unsaturated fatty alcohol, preferably oleyl alcohol.

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Macrolide compositions

This application is derived from GB 9707484.3.

This invention relates to macrolide compositions.

FK506 is a known macrolide antibiotic that is produced by Streptomyces tsukubaensis No 9993. It is also a potent immunosuppressant. The structure of FK506 is given in the appendix to the Merck Index, 11th Edition as item A5. Methods of preparing FK506 are described in EP 184162.

A large number of derivatives, antagonists, agonists and analogues of FK506, which retain the basic structure and at least one of the biological properties (for example immunological properties) of FK506, are now known. These compounds are described in a large number of publications, for example EP 184162, EP 315978, EP 323042, EP 423714, EP 427680, EP 465426, EP 474126, WO 91/13889, WO 91/19495, EP 484936, EP 532088, EP 532089, EP 569337, EP 626385, WO 93/5059 and the like. These compounds are termed collectively compounds of the FK506 class.

The macrolide may be rapamycin or an O-substituted derivative in which the hydroxy in position 40 of formula A illustrated at page 1 of WO 95/16691, incorporated herein by reference, is replaced by $-OR_1$ in which R_1 is hydroxyalkyl, hydroalkoxyalkyl, acylaminoalkyl and aminoalkyl; for example 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin and 40-O-(2-acetaminoethyl)-rapamycin. These O-substituted derivatives may be produced by reacting Rapamycin (or dihydro or deoxorapamycin) with an organic radical attached to a leaving group (for example RX where R is the organic radical which is desired as the O-substituent, such as an alkyl, allyl, or benzyl moiety, and X is a leaving group such as $CCl_3C(NH)O$ or CF_3SO_3) under suitable reaction conditions. The conditions may be acidic or neutral conditions, for example in the presence of an acid like trifluoromethanesulfonic acid, camphorsulfonic acid, p-toluenesulfonic

acid or their respective pyridinium or substituted pyridinium salts when X is $CCl_3C(NH)O$ or in the presence of a base like pyridine, a substituted pyridine, diisopropylethylamine or pentamethylpiperidine when X is CF_3SO_3.

A preferred compound is 40-0-(2-hydroxy)ethyl rapamycin (hereinafter compound A) as disclosed in WO 94/09010.

A preferred compound of the FK 506 class is disclosed in EP 427 680, e.g. Example 66a (also called 33-epi-chloro-33-desoxyascomycin) hereinafter compound B . Other preferred compounds of the FK 506 class are disclosed in EP 465 426, EP 569 337, and in EP 626 385, for example the compound of Example 6d in EP 569 337 hereinafter compound C, or the compound of Example 8 of EP 626385 hereinafter compound D.

The present applicants have found that macrolides may be unstable in topical compositions. It is believed that this instability is caused by degradation or rearrangement pathways which are not completely understood. After extensive experimental work, the applicants have found that an unsaturated fatty alcohol may be used to stabilise macrolide compositions.

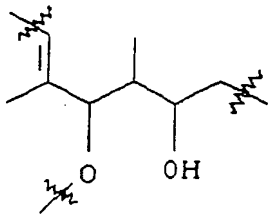
In one aspect, this invention provides the use of an unsaturated fatty alcohol in stabilising a macrolide in a pharmaceutical composition.

In another aspect, this invention provides a method of stabilising a macrolide in a pharmaceutical composition, which method comprises mixing an unsaturated fatty alcohol with the macrolide.

The unsaturated fatty alcohol may be a C_8-C_{22} alcohol, or may comprise a mixture of alcohols. The unsaturated fatty alcohol may have one, two or three double bonds. Preferably the unsaturated fatty alcohol has one double bond, and a cis configuration. Oleyl alcohol is preferred. A stabilising effect may be observed at a weight ratio of unsaturated fatty alcohol to active agent of at least about 1:5, for example 1:2 to 1:1 or greater, e.g. about 5:1.

The present applicants have found that the unsaturated fatty alcohol, e.g. oleyl alcohol, is suitable for stabilising a macrolide in a topical pharmaceutical composition. Examples of topical compositions are emulsions, e.g. creams, and suspensions as described herein.

The unsaturated fatty alcohol, e.g. oleyl alcohol, may be used to stabilise a macrolide having at least one moiety as follows:



The present applicants have found that oleyl alcohol is useful in stabilising ascomycins and compounds of the FK 506 class, for example FK 506, ascomycin and 33-epi-chloro-33-desoxyascomycin.

The compositions described in Examples 13, 14 and 19 *infra* are preferred emulsion compositions for application to mammals, e.g. humans.

For the compounds (i) [3S-[3R*[E(1S*,3S*,4S*)],4S*,-5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,-19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxy-cyclohexyl)-1-methylethenyl)]-14,16-dimethoxy-4,10,12,18,-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone,

(ii) [3S-[3R*[E(1S*,3S*,4S*)],4S*,-5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,-19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxy-cyclohexyl)-1-methylethenyl)]-14,16-dimethoxy-4,10,12,18,-tetramethyl-8-ethyl-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, and

(iii) [3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,-14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,-17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-(3-hydroxymethylcyclopentyl)-1-methylethenyl)]-14,16-dimethoxy-4,10,12,18,-tetramethyl-8-ethyl-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, topical application of concentrations of 0.01 to 1 % w/w once a day is effective in the treatment of chronic plaque psoriasis in humans. In these applications the compositions are as effective as the ultra-potent Clobetasol composition (0.05%).

The following Examples illustrate this invention.

In the Examples,

"compound 1" is the compound [3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxy-cyclohexyl)-1-methylethenyl)]-14,16-dimethoxy-4,10,12,18,-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone. This compound is better known as FK506.

"Compound 2" is the compound [3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,-14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-(3-hydroxymethylcyclopentyl)-1-methylethenyl)]-14,16-dimethoxy-4,10,12,18,-tetramethyl-8-ethyl-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone. This compound and a method of

producing it are described in EP 465426.

"Compound 3" is [3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,-19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxy-cyclohexyl)-1-methylethenyl)]-14,16-dimethoxy-4,10,12,18,-tetramethyl-8-ethyl-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone. This compound is known as ascomycin.

Compound A, compound B, compound C and compound D have the respective meanings as described above.

Chemical analysis of the active agent is undertaken using reverse phase HPLC with UV detection; λ = 210 nm. Quantification limit is 0.1% by weight.

Examples 1 to 4

Oil in water emulsions are prepared having the following compositions.

Example	1	2	3	4
Oleyl alcohol	10	10	10	10
Miglyol 812	15	15	15	15
Cetyl alcohol	4	4		
Stearyl alcohol	4	4		
Glycerol monostearate	2	2		
Sorbitan monostearate	3			
Polysorbate 20			5	
Polysorbate 60	5			
Sodium cetylstearyl sulphate		1		
Methyl Paraben	0.07	0.07	0.07	0.07
Propyl Paraben	0.03	0.03	0.03	0.03
Carbopol 974p			1	0.3
Carbopol 1382				0.7
Compound B	0.3	0.3	0.3	0.3
Citrate buffer pH 5.5	0.05	0.05		
Propylene glycol	5	5	10	10
aqueous NaOH 5% wt/vol			2.5	2.5
Water	to 100	to 100	to 100	to 100

The compositions of Examples 1 to 4 are well-tolerated on pig skin and on human skin. Assay of main degradation product is 0.1% (quantification limit) for compositions 3 and 4 after 72 hours at 70°C; the oleyl alcohol is replaced by Miglyol 812 and assay of main degradation product increases to 0.5%. No separation of components is observed when stored at room temperature for four months.

Examples 5 to 7 Oil in water emulsion compositions are prepared having 1 wt-% active agent.

Example	5	6	7
Oleyl alcohol	2.5	5	10
Miglyol 812	22.5	20	15
Cetyl alcohol	4	4	4
Stearyl alcohol	4	4	4
Glycerol monostearate	2	2	2
Sorbitan monostearate	3	3	3
Polysorbate 60	5	5	5
Methyl Paraben	0.07	0.07	0.07
Propyl Paraben	0.03	0.03	0.03
Citric acid	0.05	0.05	0.05
NaOH 1M abs. wt./100g	0.02	0.02	0.02
Propylene glycol	5	5	5
Compound B	1	1	1
Demin. water	to 100	to 100	to 100

The emulsions of Examples 5, 6 and 7 are stable and no separation of components is observed. The compositions are found to be well-tolerated on human skin. The compositions are stored at 40°C for eight weeks and chemical analysis undertaken using HPLC. Assay of main degradation product for compositions 5, 6, and 7 is 1.1%, 0.8% and 0.4% respectively.

In the compositions of Examples 1 to 7, the active agent compound B may be replaced by compound A, compound C, compound D, compound 1, compound 2 or compound 3.

Example 8

A topical suspension composition is prepared containing the following ingredients (in parts by weight) as an oil-in-water emulsion gel:

Compound B	0.3
Paraffin, thick	15
glycerol monostearate	0.3
propylene glycol	10
Carbopol 974p	0.5
Carbopol 1342	0.5
NaOH 5%	2.5
sorbic acid	0.1
water	70.8

The composition is prepared by mixing together the compound and other ingredients. The composition is subjected to stress conditions in a centrifuge for 24 hours at a temperature of up to 95°C. No degradation of the active agent is observed using HPLC.

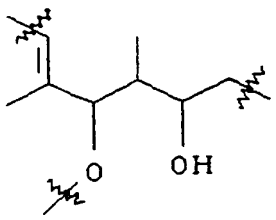
Compound B may be replaced by compound 1, 2, 3, A, C or D.

CLAIMS

1. Use of an unsaturated fatty alcohol to stabilise a macrolide in a pharmaceutical composition.

2. A method of stabilising a macrolide in a pharmaceutical composition, which method comprises mixing an unsaturated fatty alcohol with the macrolide.

3. A method as claimed in claim 2 wherein the macrolide has at least one moiety as follows



4. A method as claimed in claim 2 or claim 3 wherein the unsaturated fatty alcohol is a C_8 to C_{22} alcohol.

5. A method as claimed in claim 2, 3 or 4 wherein the weight ratio of fatty alcohol to macrolide is at least about 1:5, for example 1:2 to 1:1 or greater, e.g. about 5:1.

6. A method as claimed in claim 2, 3, 4 or 5 wherein the fatty alcohol is oleyl alcohol.

7. Use or method of stabilising a macrolide against degradation or rearrangement substantially as herein described with reference to the Examples.

The Patent Office

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Application No: GB 9818244.7
Claims searched: 1-7

Examiner: Simon M. Fortt
Date of search: 20 November 1998

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

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Int Cl (Ed.6): A61K 31/035, 31/365, 31/435, 47/10

Other: On-line: CAS-ONLINE.

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
X, P	WO 95/11039 A1	(HEXAL PHARMA) whole document particularly p 1, ll 3-7, p 7, l 9 - p 9, l 13, examples.	1, 2, 5
X	EP 0 474 126 A1	(FUJISAWA PHARMACEUTICAL) p 2, ll 5-6, p 3, l 6 - p 4, l 5, p 5, ll 24-40, examples 8 and 15.	1-6
X	EP 0 027 286 A2	(PROCTER & GAMBLE) p 4, ll 2-8, p 8, ll 2-16, example 2	1, 2, 4-6.

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.